REMARKS

Claims 1, 3, 7 and 12 have been amended. Support for the amendments to Claim 1 can be found in the Specification as filed, for example, in paragraphs [0061] and [0088]. No new matter has been introduced by these amendments. The following addresses the substance of the Office Action.

Claim Objections

The Examiner has objected to Claim 7 for missing the word "for" between the words "designed" and "the". Applicant has amended Claim 7 accordingly.

Definiteness

The Examiner has rejected Claim 3 under 35 USC §112, second paragraph, as being indefinite for reciting the phrase "having unraveled multi-drug resistance function as provided in Table 1". Applicant has amended Claim 3 to now recite "...at least 5 genes of the ABC transporter family are selected from the genes provided in Table 1." Therefore, Claim 3 is now definite, and its rejection under 35 USC §112, second paragraph should be withdrawn.

Novelty

The Examiner has rejected Claims 1-3, 6 and 15 under 35 USC §102(a) as being allegedly anticipated by Lee et al. (*J. Pharmaceut. Sci.* 2003 92:2152-2163).

> To be anticipatory under 35 U.S.C. § 102, a reference must teach each and every element of the claimed invention. *See Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1379 (Fed. Cir. 1986). "Invalidity for anticipation requires that all of the elements and limitations of the claim are found within a single prior art reference. ...There must be no difference between the claimed invention and the reference disclosure, as viewed by a person of ordinary skill in the field of the invention." *See Scripps Clinic & Research Foundation v. Genentech, Inc.*, 927 F.2d 1565 (Fed. Cir. 1991).

Lee et al. describe a microarray which has capture probes specific for MDR1 (ABC B1) and MRPs 1, 2, 3, and 6 (i.e. ABC C1, C2, C3 and C6), in other words, one member of subfamily ABC B and four members of subfamily ABC C. Lee et al. do not teach or suggest a method of using a microarray having capture probes to at least 5 ABC transporter subfamilies as recited in the currently amended Claim 1. Therefore, Claims 1-3, 6 and 15 are novel over the cited reference.

The Examiner has rejected Claims 1-3, 5, 6, 15, and 16 under 35 USC §102(b) as being allegedly anticipated by Watts et al. (*J. Pharmacol. Exp. Ther.* 2001 299:434-441).

Watts et al. describe the detection of multidrug resistance to doxorubicin. The multidrug resistant cell lines expressing MDR1 were compared with the respective sensitive cell line by isolating mRNAs, preparing cDNAs, which were then used as probes on the microarray. Figure 1 and Table 1 of Watts et al. lists several tested genes having, with the exception of MDR1 and ABC transporter 1, functions different from ABC transporters. Furthermore, Watts et al. uses a high-density microarray, as evidenced on page 435, right column under "Microarray fabrication", having probes to more than 5,000 genes on the array. Therefore, currently amended Claims 1-3, 5, 6, 15, and 16 are not anticipated by Watts et al.

For all of the above reasons, Applicants respectfully request withdrawal of all rejections under 35 U.S.C. § 102, and allowance of the pending application.

Non-obviousness

The Examiner has rejected Claims 4, and 7-14 under 35 USC §103(a) as being allegedly unpatentable over Watts et al. (*J. Pharmacol. Exp. Ther.* 2001 299:434-441) as applied to Claims 1-3, 5, 6 15, and 16 above, and further in view of Nakayama et al. (*Int. J. Cancer* 2002 101:488-495); List et al. (*Blood* 1996 87:2464-2469); Dao et al. (*Human Mol. Genet.* 1998 7:597-608); and van den Heuvel-Eibrink et al. (*Int. J. Pharmacol. Ther.* 2000 38:94-110). Applicant respectfully disagrees.

> To establish a *prima facie* case of obviousness a three-prong test must be met. First, there must be some suggestion or motivation, either in the references or in the knowledge generally available among those of ordinary skill in the art, to modify the reference. Second, there must be a reasonable expectation of success found in the prior art. Third, the prior art must reference must teach or suggest all the claim limitations. *In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991).

As discussed above, Watts et al. do not teach or suggest all the claim limitations of the currently amended Claim 1. Watts does not teach quantification of at least 5 ABC transporters on a low density microarray. The cited secondary references of Nakayama, List, Dao, and van den Heuvel-Eibrink fail to cure the deficiencies of the main reference. Nakayama teaches analysis of expression of 4 ABC transporters (MDR1, MRP1, MRP2 and BCRP) by PCR. Nakayama does not teach quantification of at least 5 ABC transporters on a low density microarray. List discloses detection of overexpression of protein, LRP, as indication for the outcome of acute myeloid leukemia, but does not teach quantification of at least 5 ABC transporters on a low density microarray. Dao discloses mouse and human versions of an

imprinted gene, which is similar to bacterial and eukaryotic polyspecific metabolite transporters and multidrug resistance pumps, but also fails to teach quantification of at least 5 ABC transporters on a low density microarray. Van den Heurvel-Eibrink discloses the relevance of MDRs in the prognosis of leukemia and mentions Pgp, MRP1 to 6, LRP/MVP and BCRP; but it also fails to teach or suggest quantification of at least 5 ABC transporters on a low density microarray. Therefore, the combinations of the cited references do not teach or suggest all the claim limitations, and the rejection of Claims 4, and 7-14 under 35 USC §103(a) should be withdrawn.

The Examiner has rejected Claims 1-3, 5, 6, 15 and 16 under 35 USC §103(a) as being allegedly unpatentable over Wang et al. (*Chinese J. Cancer Res.* 2002 14:5-10) in view of Annereau et al. (*Proc. Amer. Assoc. Cancer Res.* 2003 44:796-797, abstract # 3992). More specifically, the Examiner stated that it would have been *prima facie* obvious at the time the invention was made to a person with an ordinary skill in the art to have incorporated the array disclosed by Annereau into the analysis of gene expression changes in resistant cells treated with an anti-cancer drug as disclosed by Wang.

Wang et al. describes gene expression profiling in multidrug resistant KB cells using high density microarrays (having 12,720 PCR products), and specifically mentions overexpression of MDR1 and MRPs. Annereau et al. describes using a high-density microarray (over 18000 probes) to detect the expression of 36 members of the ABC-transporter superfamily in drug resistant cells. The combination of these references does not teach or suggest using a low-density microarray (no more than 3,000 probes) having capture probes specific for at least 5 ABC-transporter subfamilies, is silent about a change of the gene expression of at least 5 ABC transporters by a factor of at least about 1.5 as compared to a reference being indicative of the development and/or existence of resistance of cells to the tested substance.

In conclusion, none of the combinations of the cited references teach or suggest selecting 5 ABC transporters from 5 different subfamilies of ABC transporters to perform the determination of the resistance of cells to the action of an active substance using a low-density microarray having less than 3,000 probes.

Because of these deficiencies, Applicants submit that the PTO has failed to articulate a *prima facie* case of obviousness, and as such, the present rejection of Claims 1-16 under 35 U.S.C. 103 should be withdrawn.

CONCLUSION

Applicants have endeavored to address all of the Examiner's concerns as expressed in the outstanding Office Action. Accordingly, amendments to the claims, the reasons therefor, and arguments in support of the patentability of the pending claim set are presented above. In light of the above amendments and remarks, reconsideration and withdrawal of the outstanding rejections is specifically requested. If the Examiner finds any remaining impediment to the prompt allowance of these claims that could be clarified with a telephone conference, the Examiner is respectfully requested to initiate the same with the undersigned.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: January 18, 2007

By: _____

Marina L. Gordey
Registration No. 52,950
Agent of Record
Customer No. 20,995
(805) 547-5580

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